Mechanistic Investigation of the Ring Opening in the *Staudinger* Cycloaddition Involving Ketenes with Electron-Withdrawing Substituents

by **Shanyan Mo** and **Jiaxi Xu***

State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, P. R. China (phone/fax: +86-10-64435565; e-mail: jxxu@mail.buct.edu.cn)

The cycloaddition of ketenes and imines (*Staudinger* cycloaddition) is a general method for the synthesis of various β-lactams. However, reactions of imines and ketenes with electron-withdrawing substituents produce α,β-unsaturated alkenamides, ring-opening products of the intermediates generated from imines and the ketenes, even as sole products, besides the desired β-lactams. The mechanism of the formation of α,β-unsaturated alkenamides was investigated. The results indicate that the α,β-unsaturated alkenamides are generated *via* a base-induced C=C bond isomerization followed by electrocyclic ring opening of the formed azacyclobutenes (=1,2-dihydroazetes; *cf. Scheme 3*).

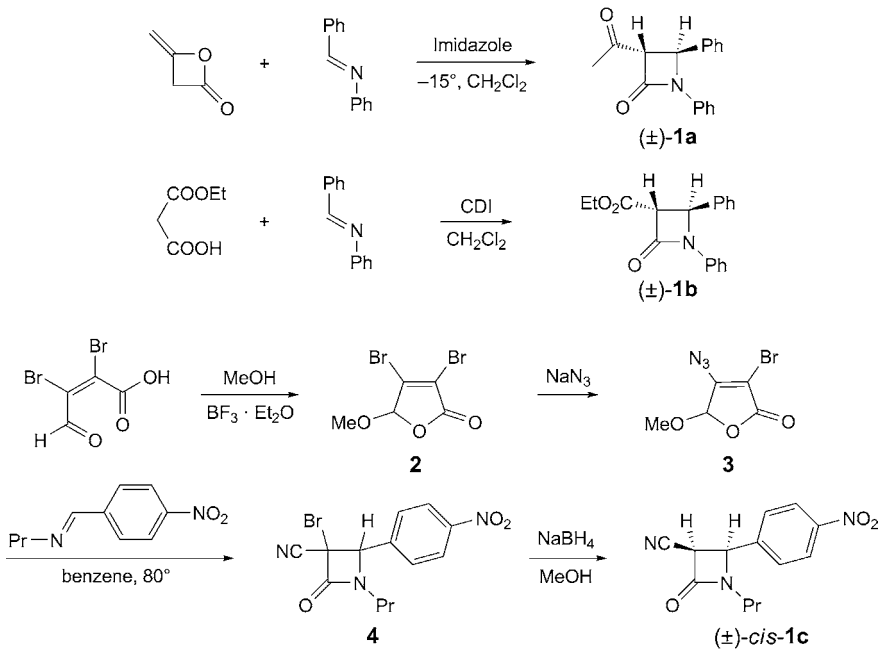
Introduction. – The β-lactam structure is the fundamental structural skeleton of the important and widely used β-lactam antibiotics [1] and key intermediates in organic and pharmaceutical synthetic chemistry [2]. To date, numerous methods have been developed for the synthesis of β-lactams due to their important role in pharmaceutical chemistry [2]. Among them, the *Staudinger* cycloaddition, *i.e.*, the formation of azetidin-2-ones from ketenes and imines, is one of the most versatile methods for the synthesis of β-lactam derivatives with a clear configuration control [3]. However, the method has been seldom applied to the synthesis of β-lactams with electron-withdrawing substituents, such as acyl [4], COOH or derivative thereof [5], and CN [6], especially to the synthesis of 3-monosubstituted β-lactams with electron-withdrawing substituents. Indeed, α,β-unsaturated alkenamides, *i.e.*, ring-opening products of the intermediates were obtained from imines and ketenes with electron-withdrawing substituents, even as sole products, besides the desired β-lactams in most cases [7]. Although the mechanism of the formation of α,β-unsaturated alkenamides has been discussed previously [7d][7e][8], it is still unclear. This limits the application of the *Staudinger* cycloaddition for the preparation of β-lactams with electron-withdrawing substituents. The latter are key intermediates or precursors for the synthesis of β-lactam antibiotics and their analogs for drug production or discovering. To understand and thereby avoid the side reaction generating alkenamides, with the aim to utilize the *Staudinger* cycloaddition efficiently in the synthesis of β-lactams with electron-withdrawing substitutents, we report below on the mechanism of the formation of α,β-unsaturated alkenamides.

Results and Discussion. – Analyzing the structural features of α,β-unsaturated alkenamides, it might be assumed that they are formed from certain enolic isomers of

the β-lactams generated from imines and the ketenes with electron-withdrawing substituents by a conrotatory 4e electrocyclic ring opening. Thus, to verify this assumption, we hoped to prepare model β-lactams with π-acceptor substituents at C(3) and to investigate their reactions in the presence of different bases.

Therefore, the 3-substituted β-lactams 3-acetylazetidin-2-one **1a**, ethyl 2-oxazetidine-3-carboxylate **1b**, and 2-oxazetidine-3-carbonitrile **1c** were prepared by reported procedures (*Scheme 1*). *trans*-3-Acetylazetidin-2-one (±)-**1a** was obtained from the reaction of diketene and *N*-benzylideneaniline (= *N*-(phenylmethylene)benzenamine) in the presence of 1*H*-imidazole in CH_2Cl_2 [9]. Ethyl carboxylate (±)-**1b** was synthesized from the reaction of the ethyl half ester of malonic acid and *N*-benzylideneaniline in the presence of di(1*H*-imidazol-1-yl)methanone (CDI) in CH_2Cl_2 [10]. The *cis*-carbonitrile (±)-*cis*-**1c** was prepared by referring to *Moore*'s method [6e]. Mucobromic acid (= (2*Z*)-2,3-dibromo-4-oxobut-2-enoic acid) was first treated with boron trifluoride etherate solution in MeOH to convert it to 3,4-dibromo-5-methoxyfuran-2(5*H*)-one (**2**) [11], which further reacted with sodium azide to afford 4-azido-3-bromo-5-methoxyfuran-2(5*H*)-one (**3**). The latter and *N*-(4-nitrobenzylidene)propan-1-amine were refluxed in benzene to give rise to the 3-bromo-2-oxoazetidine-3-carbonitrile **4**. Although it was reported that 3-chloro-2-oxoazetidine-3-carbonitriles were smoothly reduced to 2-oxoazetidine-3-carbonitriles with Zn/AcOH as reductant [6c][12], 3-bromo-2-oxoazetidine-3-carbonitrile **4** produced a messy product mixture under the same reduction conditions. Fortunately, the Br-substituent could be removed successfully from **4** with sodium borohydride in MeOH to yield β-lactam (±)-

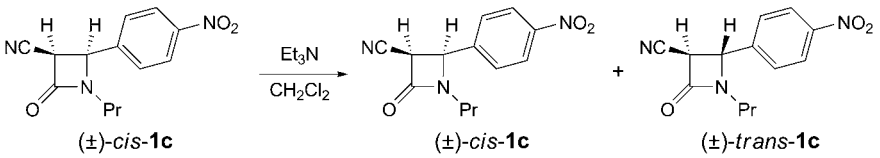
Scheme 1. *Synthesis of β-Lactams with π-Electron-Withdrawing Substituents at C(3)*



cis-**1c**. Its relative configutation was determined on the basis of its vicinal H,H-coupling constant. *Moore* and co-workers confirmed previously that *cis*-2-oxoazetidine-3-carbonitriles are major products in the reduction of 3-halo-2-oxoazetidine-3-carbonitriles with Zn/AcOH as reductant [6c][12].

To investigate the electrocyclic ring-opening reactions, all synthetic model β-lactams were dissolved in different solvents, *e.g.*, in toluene, CH_2Cl_2, and THF, which are usually used in *Staudinger* cycloadditions, and the resulting solutions were heated under reflux and stirring in the presence of bases, such as Et_3N, pyridine, and even strong bases such as NaH. In all cases, no α,β-unsaturated alkenamide derivative was observed, and most of the β-lactams remained unchanged, except for (±)-*cis*-**1c**, which was converted to the more stable (±)-*trans*-**1c** under reflux in the presence of base (*Scheme 2*). The results (*Table*) indicate that if β-lactams with π-electron-withdrawing substituents at C(3) are generated in the reactions, they cannot undergo the electrocyclic ring-opening reaction to produce the corresponding α,β-unsaturated alkenamides under basic reaction conditions.

Scheme 2. *Conversion of (±)-*cis-**1c** *to (±)-*trans-**1c** *in the Presence of Et_3N*



(±)-*cis*-**1c** (±)-*cis*-**1c** (±)-*trans*-**1c**

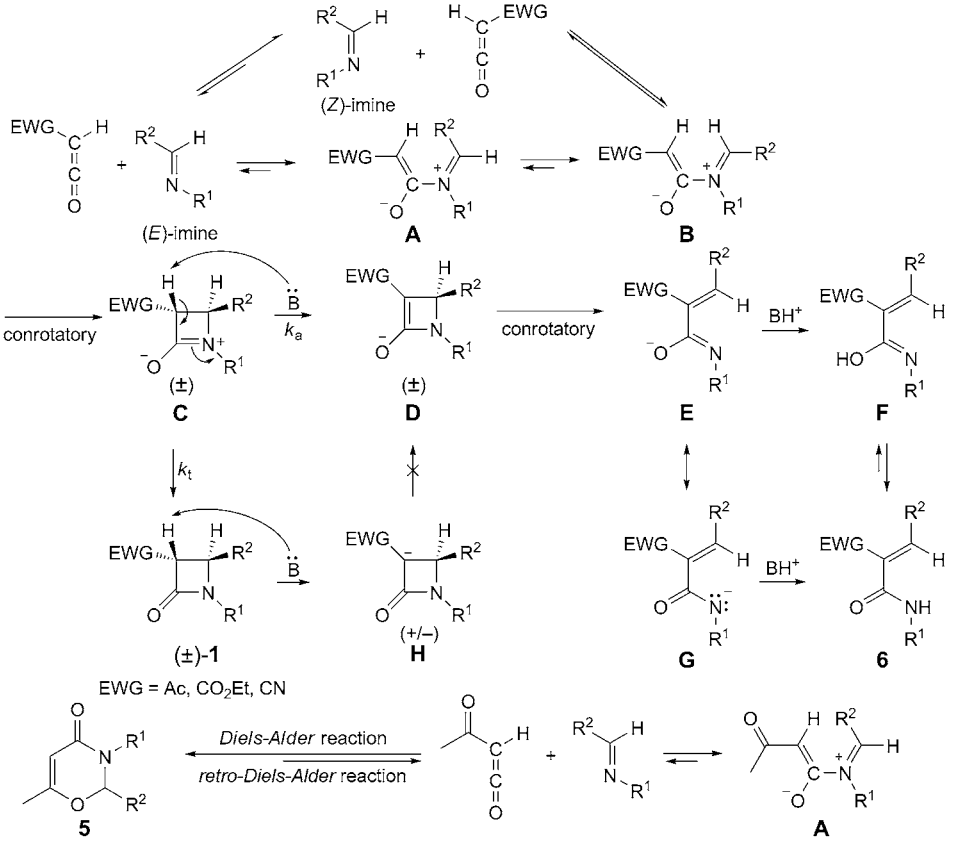
Table. *Reaction of β-Lactams with π-Acceptor Substituents at C(3) in the Presence of Base*

β-Lactam	Base	Solvent	Temp. [°]	Time [d]	Product(s)	Ratio (*cis*/*trans*)
(±)-**1a**	Et_3N	toluene	110	2	(±)-**1a**	
(±)-**1a**	NaH	THF	66	1.5	(±)-**1a**	
(±)-**1b**	Et_3N	toluene	110	2	(±)-**1b**	
(±)-*cis*-**1c**	Et_3N	toluene	110	1	(±)-*cis*/*trans*-**1c**	45 : 55
(±)-*cis*-**1c**	Et_3N	CH_2Cl_2	25	0.5	(±)-*cis*/*trans*-**1c**	40 : 60
(±)-*cis*-**1c**	NaH	THF	66	1	(±)-*cis*/*trans*-**1c**	0 : 100
(±)-*cis*-**1c**	pyridine	toluene	110	6	(±)-*cis*/*trans*-**1c**	70 : 30

A survey of the literature showed that several acetylketene precursors, including 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one [7e], diketene [7c], acetoacetyl chloride [5b], and AcCl [7b], reacted with some imines to give rise to 2,3-dihydro-6-methyl-4*H*-1,3-oxazin-4-ones **5**, 2-alkylideneacetoacetamides **6**, and 3-acetylazetidin-2-ones **1**, or their mixtures (*cf. Scheme 3*). Cyanoacetyl chloride reacted with linear imines in the presence of Et_3N to afford 2-cyanoalk-2-enamides [7a]. However, with cyclic imines, cyanoacetylchloride yielded β-lactam products [3c]. Futhermore, 2-cyanoalkanoyl chlorides (except for cyanoacetyl chloride) gave rise to β-lactam products when they reacted with linear imines [13].

On the basis of the above results, we are inclined to consider that the mechanism of the formation of α,β-unsaturated alkenamides is as follows (*Scheme 3*). An (*E*)-imine attacks the generated ketene with an electron-withdrawing substituent (EWG) from its less hindered *exo*-side in the reaction system to yield zwitterionic intermediate **A**,

Scheme 3. *Proposed Reaction Mechanism of the Reaction of Imines and Ketenes with Electron-Withdrawing Substituents*



which isomerizes to form the more stable zwitterion **B** because ring closure of intermediate **A** to afford the *cis*-β-lactam directly is unfavorable due to the electron-withdrawing substituent [3a]. There exists another possibility to generate intermediate **B** *via* N-inversion–isomerization of the (*E*)-imine to the (*Z*)-imine, which attacks the ketene with an electron-withdrawing substituent from its *exo*-side. The intermediate **B** undergoes conrotatory ring closure to form the azaenolate **C** of the *trans*-β-lactam, which converts to the enolate **D** by base-induced deprotonation at the α-position of **C**. Intermediate **D** undergoes a conrotatory electrocyclic ring opening to produce amide enolate **E** which, on protonation by the conjugated acid HB, gives **6**, possibly *via* **F**, or which tautomerizes to amide anion **G** and following protonation by the conjugated acid HB gives **6**. On the other hand, the intermediate **C** tautomerizes directly to the *trans*-β-lactams (±)-**1**. The rate constants k_a (the rate constant of the acid-base reaction) and k_t (the rate constant of the tautomerization from **C** to *trans*-β-lactam (±)-**1**) control the ratio of the products **6** and (±)-**1**. For an enolate **C** with a strong electron-withdrawing substituent, the H-atom at C(3) is more acidic. Thus, the intermediate **C** is

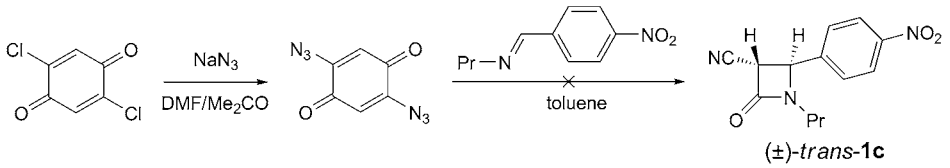
predominantly converted to **D** in the presence of base ($k_a >> k_t$), resulting in the formation of α,β-unsaturated alkenamide **6**. The azaenolate **C** with an electron-withdrawing substituent can produce both the α,β-unsaturated alkenamide **6** and the *trans*-β-lactam (±)-**1** if k_a is close to k_t. However, the H–C(3) of β-lactams without an eletron-withdrawing substituents is less acidic. Intermediate **A** predominantly converts to β-lactams (±)-**1** if $k_a << k_t$. Once the β-lactam is generated, it cannot convert to the α,β-unsaturated alkenamide **6**, even by carbanion formation at C(3) because this carbanion **H** is more stable than the enolate **D**.

Furthermore, 3-nitro-β-lactams are prepared by nitration of lithiated β-lactams at C(3) with propyl nitrate. In these preparations, no ring-opening reaction was observed, revealing that 3-nitro-β-lactam carbanions cannot convert to the corresponding α,β-unsaturated nitroalkenamides [14][15].

Acetylketene and imines can also undergo a *Diels–Alder* cycloaddition to afford 2,3-dihydro-6-methyl-4*H*-1,3-oxazin-4-ones **5**, which can undergo, on heating, a *retro-Diels–Alder* reaction to regenerate acetylketene and imines. They can react to form intermediates **C**, which further convert to α,β-unsaturated alkenamides **6** and *trans*-β-lactams (±)-**1** as final products (*Scheme 3*). This provides a rational explanation for the reported experimental results [7].

Moore's group reported that 2,5-diazidobenzo-1,4-quinone derivatives can serve as cyanoketene precursors and thus undergo cycloadditions with imines under thermal conditions in the absence of base [6a–6e]. To verify our proposed mechanism, we hoped to realize the synthesis of 2-oxoazetidine-3-carbonitrile (±)-*trans*-**1c** *via* thermal cycloaddition of *N*-(nitrobenzylidene)propan-1-amine and cyanoketene, generated from 2,5-diazido-1,4-benzoquinone under heating (*Scheme 4*); under the conditions of thermal cycloaddition, no base exists, hence the 3-carbonitrile was assumed to be generated. Thus, 2,5-diazido-1,4-benzoquinone was prepared from 2,5-dichloro-1,4-benzoquinone with sodium azide [16] and treated with *N*-(nitrobenzylidene)propan-1-amine in refluxing toluene (*Scheme 4*). However, no cycloaddition was observed although 2,5-diazido-1,4-benzoquinone decomposed completely.

Scheme 4. *Reaction of 2,5-Diazido-1,4-benzoquinone and* N-*(Nitrobenzylidene)propan-1-anime*



(±)-*trans*-**1c**

Conclusions. – The mechanism of the formation of α,β-unsaturated alkenamides in the *Staudinger* cycloaddition of imines and ketenes with electron-withdrawing substituents was investigated. The results indicate that the α,β-unsaturated alkenamides were generated *via* the base-promoted C=C bond isomerization and electrocyclic ring-opening reaction of formed azacyclobutenes (= 1,2-dihydroazetes) from the intermediates generated from imines and ketenes with electron-withdrawing substituents.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh); petroleum ether (60–90°) and AcOEt as eluents. M.p.: uncorrected. ^{1}H- and ^{13}C-NMR Spectra: at 400 MHz in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. IR Spectra: in KBr. HR-MS: LC/MSD TOF mass spectrometer; in *m*/*z*.

(±)-trans-*3-Acetyl-1,4-diphenylazetidin-2-one* ((±)-**1a**). Diketene (2.1 g, 25 mmol) in CH_2Cl_2, (10 ml) was added dropwise to a soln. of *N*-(benzylidene)aniline (906 mg, 5 mmol) and 1*H*-imidazole (525 mg, 7.5 mmol) in CH_2Cl_2, (10 ml) at −15°. The resulting soln. was stirred overnight. After evaporation, the residue was purified by CC (SiO_2, petroleum ether AcOEt 6 : 1 → 1 : 1): 790 mg (59.5% of (±)-**1a**). Colorless crystals. M.p. 74–76°. IR: 1754 (C=O), 1717 (C=O). ^{1}H-NMR: 2.38 (*s*, Me); 4.13 (*d*, *J* = 2.4, CH); 5.47 (*d*, *J* = 2.4, CH); 7.04–7.07 (*m*, 1 arom. H); 7.22–7.27 (*m*, 4 arom. H); 7.33–7.38 (*m*, 5 arom. H). ^{13}C-NMR: 29.8; 55.5; 71.8; 117.0; 124.2; 126.0; 127.3; 128.0; 129.0; 129.2; 136.5; 137.1; 160.2; 198.7. HR-ESI-MS: 266.1177 ($[M+H]^+$, $C_{17}H_{16}NO_2^+$; calc. 266.1176).

(±)-Ethyl trans-*2-Oxo-1,4-diphenylazetidine-3-carboxylate* ((±)-**1b**). A soln. of 3-ethoxy-3-oxopropanoic acid (15.4 g, 20 mmol) and di(1*H*-imidazol-1-yl)methanone (2.64 g, 60 mmol) in CH_2Cl_2, (100 ml) was stirred at r.t. for 1 h. To the soln. was added *N*-(benzylidene)aniline (3.62 g, 20 mmol) in CH_2Cl_2, (40 ml) while stirring. The resulting mixture was stirred for another 1 h. After evaporation, the residue was purified by CC (SiO_2, with petroleum ether/AcOEt 30 : 1 → 20 : 1): 1.8 g (30.5%) of (±)-**1b**. Colorless crystals. M.p. 92–93° ([10]: m.p. 87–89°). IR: 1767 (C=O), 1713 (C=O). ^{1}H-NMR (200 MHz): 1.33 (*t*, *J* = 7.2, *Me*CH_2); 3.98 (*d*, *J* = 2.7, CHCO); 4.30 (*q*, *J* = 7.2, MeCH_2); 5.34 (*d*, *J* = 2.7, CHN); 7.05–7.42 (*m*, 10 arom. H). ^{13}C-NMR (75.5 MHz): 14.1; 57.5; 62.1; 63.5; 117.1; 124.3; 126.1; 128.96; 129.03; 129.2; 136.2; 137.1; 159.2; 166.2.

*3,4-Dibromo-5-methoxyfuran-2(5*H*)-one* (**2**). $Et_2O \cdot BF_3$ (1.26 ml, 10.2 mmol) was added to a soln. of mucobromic acid (2.58 g, 10 mmol) in MeOH (40 ml), and the resulting soln. was stirred at r.t. for 2 d. After evaporation, the residue was dissolved in CH_2Cl_2, (20 ml), the resulting soln. washed with sat. aq. Na_2CO_3 soln. (3 × 20 ml), and the org. phase dried (Na_2SO_4) and concentrated: 2.43 g (90%) of **2**. White solid. M.p. 49–50° ([11]: m.p. 52°).

*4-Azido-3-bromo-5-methoxyfuran-2(5*H*)-one* (**3**). To a soln. of **2** (2.43 g, 8.94 mmol) in MeOH (20 ml), NaN_3 (581 mg, 8.94 mmol) was slowly added under stirring at 0°, and the resulting soln. was stirred for 1 h. Addition of H_2O and filtration gave 1.65 g (78.9%) of **3**. White solid. M.p. 74–75°.

3-Bromo-2-(4-nitrophenyl)-4-oxo-1-propylazetidin-3-carbonitrile (**4**). A soln. of **3** (468 mg, 2 mmol) and *N*-(4-nitrobenzylidene)propan-1-amine (294 mg, 1.53 mol) in anh. benzene (10 ml) was stirred overnight at 80°. After evaporation, the residue was purified by CC (SiO_2, petroleum ether/AcOEt 10 : 1 → 5 : 1): 469 mg (90%) of **4**. Colorless crystals. M.p. 120–121°. IR: 2235 (CN), 1790 (C=O). ^{1}H-NMR: 0.97 (*t*, *J* = 7.6, Me); 1.53–1.72 (*m*, MeCH_2); 2.97 (*ddd*, *J* = 5.6, 7.6, 14.0, 1 H, CH_2N); 3.57 (*ddd*, *J* = 7.6, 7.6, 14.0, 1 H, CH_2N); 5.06 (*s*, CH); 7.62 (*d*, *J* = 8.4, 2 arom. H), 8.38 (*d*, *J* = 8.4, 2 arom. H). ^{13}C-NMR: 11.2; 20.5; 44.1; 45.3; 68.8; 111.7; 124.7; 128.4; 138.1; 149.3; 156.6. HR-ESI-MS: 338.0140 ($[M+H]^+$, $C_{13}H_{13}BrN_3O_3^+$; calc. 338.0135).

*(±)-*cis-*2-(4-Nitrophenyl)-4-oxo-1-propylazetidin-3-carbonitrile* ((±)-*cis*-**1c**). To a soln. of **4** (338 mg, 1 mmol) in MeOH (10 ml), H_2O (5 ml) was added, and the resulting soln. was cooled to 0°. $NaBH_4$ (46 mg, 1.2 mmol) was portionwise added, and the resulting soln. was stirred for 2 h. After evaporation, the residue was purified by CC (SiO_2, petroleum ether/AcOEt 3 : 1 → 1 : 1): 181 mg (70%) of (±)-*cis*-**1c**. Colorless crystals. M.p. 136–138°. IR: 2247 (CN), 1774 (C=O). ^{1}H-NMR: 0.92 (*t*, *J* = 7.6, Me); 1.47–1.65 (*m*, CH_2); 2.95 (*ddd*, *J* = 6.0, 8.0, 14.0, 1 H CH_2N); 3.57 (*ddd*, *J* = 7.6, 7.6, 14.0, 1 H, CH_2N); 4.47 (*d*, *J* = 5.4, CHN); 4.99 (*d*, *J* = 5.4, CHCO); 7.58–7.60 (*m*, 2 arom. H); 8.34–8.37 (*m*, 2 arom. H). ^{13}C-NMR: 11.4; 20.7; 43.9; 46.0; 56.0; 112.3; 124.5; 128.3; 140.0; 148.9; 157.7. HR-ESI-MS: 260.1027 ($[M+H]^+$, $C_{13}H_{14}N_3O_3^+$; calc. 260.1030).

Reaction of β-Lactams with π-Acceptor Substituents at C(3) in the Presence of Base: General Procedure. The β-lactam (0.1 mmol) was added to the desired solvent (see *Table*). The selected base

(1.5 mmol) was added and the resulting soln. was refluxed for a period of time (TLC monitoring). If reaction occurred, the ratio of products was determined by ^{1}H-NMR analysis of the crude reaction mixture.

(±)-trans-*2-(4-Nitrophenyl)-4-oxo-1-propylazetidin-3-carbonitrile* ((±)-*trans*-**1c**). To a soln. of (±)-*cis*-**1c** (104 mg, 0.4 mmol) in CH_2Cl_2, (5 ml) was added Et_3N (80 mg, 0.79 mmol). The resulting soln. was stirred for 1 h. After evaporation, the residue was purified by CC (SiO_2, petroleum ether/AcOEt 3 : 1 → 1 : 1): (±)-*trans*-**1c** (52 mg, 50%), besides recovered (±)-*cis*-**1c** (30 mg). (±)-*trans*-**1c**: Colorless crystals. M.p. 97 – 98°. IR: 2247 (CN), 1771 (C=O). ^{1}H-NMR: 0.94 (*t*, *J* = 7.4, Me); 1.50 – 1.61 (*m*, CH_2); 2.91 (*ddd*, *J* = 7.0, 7.0, 14.2, 1 H, CH_2N); 3.46 (*ddd*, *J* = 7.6, 7.6, 14.2, 1 H CH_2N); 3.81 (*d*, *J* = 2.6, CHN); 4.90 (*d*, *J* = 2.6, CHCO); 7.59 (*d*, *J* = 8.6, 2 arom. H), 8.38 (*d*, *J* = 8.6, 2 arom. H). ^{13}C-NMR: 11.4; 20.8; 43.9; 46.8; 58.0; 113.3; 124.8; 127.5; 141.7; 148.9; 157.4. HR-ESI-MS: 260.1029 ($[M+H]^+$, $C_{13}H_{14}N_3O_3^+$; calc. 260.1030).

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